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EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	**PAPER NUMBER**
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/17/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

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Office Action Summary	Application No.	Applicant(s)	
	10/656,873	FISHMAN ET AL.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 8-32* is/are pending in the application.

4a) Of the above claim(s) *8-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 20-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Currently, claims 1-6, 8-20, and newly added claims 21-32 are pending in the instant application. Claims 8-19 are withdrawn from consideration as being drawn to a non elected inventions. Claims 1-6, and 20-32 are currently under examination. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. The following rejections are either newly applied, as necessitated by amendment, or are reiterated. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is FINAL.

Priority

2. Applicants claim for priority to provisional application 60/175,787, filed 1/12/2000 is acknowledged. It is noted, however, that the '787 application does not disclose the genotype of the pickwick mutation.

Claim Rejections - 35 USC § 112

3. Claims 1-6, 20 and newly added claims 21-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements

and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The claims are broadly drawn to a method for determining whether a test subject from any source, including mammals and humans, has, is at risk of developing, may have or may be at risk of developing, or has an increased likelihood of *any* titin related disease or condition of the heart by detecting *any* mutation from a titin gene, including a naturally occurring gene. The claims are further drawn to a method of facilitating the etiology of an existing heart disease or condition by detecting *any* mutation from a titin gene , from any source. The claims are further limited to heart failure as well as any mutation in a cardiac specific exon as well as the N2B exon of titin.

The nature of the invention, therefore, requires the knowledge of predictive associations between any mutation in a titin gene from any subject and any condition or disease of the heart.

The amount of direction or guidance and presence and absence of working examples:

The specification teaches that heart disease is a general term used to describe different heart conditions. The specification teaches that risk factors include coronary artery disease, hypertension, valvular heart disease, cardiomyopathy, disease of the heart muscle, obesity,

diabetes, and family history of heart failure (see page 1). The specification teaches that during a mutation screening of zebra fish, a phenotype resulting from mutation of the titin gene was observed which was similar to mammalian heart failure (page 1).

The specification teaches that the claimed recitation of a "titin gene" is drawn to a nucleic acid that encodes a titin protein or polypeptide that has 45%, 60%, 75% and 90% identity to the sequence of human or zebra fish titin molecules (see p. 3). Such a recitation encompasses mutants, allelic variants, and homologs of titin from any source, which have not been taught or described in the specification. The specification further defines "titin related disease or condition" to mean a disease or condition that results from an inappropriately high or low expression of a titin gene or a mutation in a titin gene that alters the biological activity of a titin nucleic acid or polypeptide. Therefore, the recitation encompasses any substitution, deletion or insertion in any titin gene. The specification teaches that the methods include diagnostic assessment of heart disease, heart failure (page 8, first full para), congestive heart failure, and coronary artery diseases or conditions associated with valve formation defects (page 9). The specification, however, has only taught a single mutation in the N2B exon of titin that was found in zebra fish embryos characterized with a weak heartbeat (see p. 20). Further, the whereabouts of this mutation in the N2B exon are unclear as the specification only teaches that identification of a T-G transition in the *pikm171* allele was found which resulted in a change of leucine in the IS3 fragment of N2B domain into a stop codon. The specification, however, does not teach at which leucine residue this mutation occurs. In addition, the specification does not define the specific genotype of the *pickwick* mutation. The specification recites "a mutation in a cardiac specific exon, such as the N2B exon, e.g. the *pickwick* mutation" (see p. 2, lines 9-10), thus it is

unclear from this recitation or the teachings in the specification as to what is encompassed by the *pickwick* mutation. Xu (Xu et al; Nature Genetics, vol. 30, pages 205-209; 2002) teaches that there are multiple alleles in the *pik* complementation group (see abstract), however the specification provides no description of the other alleles. The specification has only taught a single mutation that appears to be associated with a weak heart beat in zebra fish embryos, but the specific genotype of this mutation is not taught.

The specification has not taught any working examples of any other mutations in the titin gene from zebra fish, or any other species including any mammals or human population, which is associated with a titin related disease or condition of the heart. Further, the specification has not taught an association between the pickwick mutation and any of the diseases or conditions which is encompassed by the claims, in zebra fish or in any other species, including mammals. Although the specification teaches that the pickwick mutation is associated with a weak heartbeat in zebra fish, which may be similar to mammalian heart failure, such is not necessarily diagnostic of mammalian heart failure, let alone any disease or condition of the heart in any mammal or human. While a weak heart beat may lead to heart failure, there are other causes for heart failure including coronary artery disease, hypertension and diabetes (as taught by the specification at page 1). Therefore, while coronary artery disease, hypertension, or diabetes may all lead to heart failure, a mutation which is associated with any one of these disease or conditions is not necessarily *diagnostic* of another. Each represents a specific disease which have different symptoms and causes. The specification has not established a universal correlation between any mutation in any titin gene and an association with any disease or condition of the heart as is broadly claimed.

The specification does not teach or provide any guidance as to which regions or amino acids in the titin gene would be affected to provide for the diagnostic associations set forth in the claims. The specification does not teach or provide any guidance as to what information one of skill in the art would conclude, as to the etiology of an existing heart disease or condition, from the fact that a subject possessed any mutation in a titin gene. The specification teaches a single phenotype, the pickwick mutation, but does not teach what this position is in the titin gene from zebra fish or any other species, nor does it teach if the T to G tranversion even exists in other species. The specification does not teach what other positions within the titin gene of zebra fish or the titin gene from other species would provide the same phenotype or whether a polymorphism would have the same effect in another gene. The specification provides no guidance as to conserved and nonconserved positions in titin from different species. The specification provides no guidance regarding which specific amino acids, domains, or regions within titin would be "informative" nor what disease etiology they would be "informative" for.

The state of the prior art and the predictability or unpredictability of the art:

While the claims are broadly drawn to detecting any mutation in any region of the titin gene and association to any disease or condition of the heart, Garvey (Garvey et al; Genomics, vol. 79, pages 146-149, 2002) teaches that titin is differentially spliced with a cardiac muscle isoform N2B and a skeletal muscle isoform N2A (see page 146, col. 2). Garvey teaches a mutation in mouse titin which disrupts the N2A domain but which was not associated with any cardiac muscle pathology. Accordingly, it is clear that a mutation or polymorphism in "any region" of titin is not universally correlative of an association with heart disease. This lack of

universal association is also true of the cardiac isoform of human titin. For example, Itoh-Satoh et al (Biochemical and Biophysical Research Communications, vol. 291, pp 385-393; 2002) teach a mutation in the titin gene which may be associated with Dilated Cardiomyopathy (p. 387, col. 2, lines 7-13), but another mutation, Arg328Cys, was found in healthy control subjects, indicating that it is a polymorphism not related with DCM (col. 2, lines 3-5). Additionally, Siu (Siu et al; Circulation, March 1999, vol. 99, pages 1022-1026) teaches that five variations were found in the N2B region of human titin, including 3 which did not alter the protein sequence and 2 which did, but that were determined to not be disease-causing mutations (page 1025, col. 2).

The prior art provides no analysis of mutations in titin and comparisons to similar positions across species. The prior art does not provide any analysis of titin function with regard to mutational analysis nor does it provide any indication of mutations in regions of titin which would be associated with heart disease or conditions. The post filing date art of Itoh-Satoh teaches a number of mutations in human titin, but also provides alignments across different species. As seen in figures 1 and 2, the amino acid positions are not necessarily conserved across different species, especially noting the differences found in the Z line region between chicken and human titin sequences.

The level of skill in the art:

The level of skill in the art is deemed to be high.

The quantity of experimentation necessary:

The teachings of the specification are insufficient to provide one of skill in the art with a predictable correlation that any substitution, deletion or insertion in the titin gene, or more specifically the IS3 fragment of N2B would result in a weak heartbeat in zebra fish embryos or any other species. The single point mutation, whose location is not taught, set forth in the specification also does not provide one of skill in the art with a predictable correlation between any mutations in any titin gene from any source and any disease or condition of the heart, including heart failure. The specification lacks sufficient guidance to enable one of skill in the art to make or use the invention as broadly as it is claimed, without undue experimentation.

To practice the invention as broadly as it is claimed the skilled artisan would have perform an enormous amount of research to mutate each position of the titin gene from each species, which encodes a protein which is on the order of 27,000 amino acids, and perform functional analysis to determine which positions and what alterations are associated with diseases or conditions of the heart, as well as which positions would be informative regarding etiology of a disease or condition of the heart. The skilled artisan would then be required to perform a large study which included subjects affected with a large number of different diseases or conditions of the heart as well as controls and to screen such for any mutation in a titin gene to determine which mutations were predictably correlative of disease and which were not, as well as what information they would be able to provide. Such analysis would consist of unpredictable trial and error research projects as evidenced by the art cited above. An enormous amount of inventive effort would be required for these research projects, with each intervening step not being predictive of any particular outcome. For example, given the lack of guidance in the

specification and the art, the skilled artisan would not have been able to predict the mutations taught by Itoh-Satoh nor would the skilled artisan have been able to distinguish which of the mutations taught by Siu and Itoh-Satoh are associated with disease as opposed to those that are not.

It is known for nucleic acids as well as proteins that a single nucleotide or amino acid change or mutation can alter the function of the biomolecule in some instances. Given the lack of guidance in the art at the time the invention was made as well as the lack of guidance in the specification, the effects of these changes are unpredictable as to which ones have a significant effect versus not. The specification has not provided the skilled artisan with any teaching or guidance as to which nucleotide or amino acid positions in the titin gene would be responsible for normal or aberrant activity of the titin protein. Without such, the skilled artisan would further be unable to predictably correlate which mutations would have and would not have an effect on the function or activity of any titin protein. The art exemplifies this unpredictability.

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

4. The response traverses the rejection. The response asserts that the amendment to claim 1 to specify a "naturally occurring titin gene" overcomes the examiner's basis for rejection

regarding the definition of "titin gene" given in the specification. The amendment and argument have been thoroughly reviewed but were not found persuasive. The term "naturally occurring titin gene" encompasses titin genes from any species. In the previous office action, the examiner stated that the term "titin gene" as defined by the specification, encompasses mutants, allelic variants, and homologs of titin from any source. "Any source" includes any species, which is still an extremely large number of possible allelic variants, mutants, and homologs of any titin gene, which is encompassed by the amended claims and does not narrow the scope of the claims to overcome the rejection.

The response further asserts that the analysis of the sequences of titin genes from patients and the correlation of any detected mutations with a disease or condition of the heart would not require undue experimentation as is shown by the teachings of Satoh (cited in the 102(a) rejection) which used standard methods of analysis such as PCR. This argument has been thoroughly reviewed but was found unpersuasive. The office action has not disputed that genetic analysis uses methods known in the art. However, the scope of the instantly pending claims sets forth that any mutation in the titin gene from any source is diagnostic for or predictive of disease risk, or provides information regarding etiology of any heart disease or condition. However, the scope of the teachings in the specification is not commensurate in scope with the claimed invention, as the specification provides not teaching or guidance as to which specific mutations in titin from any species, including humans, is associated with a titin related disease or condition of the heart. The full scope of the claimed invention is much broader, such that the single mutation in zebrafish taught in the specification does not establish a predictable correlation that *any* mutation in *any* titin gene, variant, or homolog, is associated with *any* disease or condition of

the heart, including heart failure, or provides information as to the etiology of a disease or condition of the heart to overcome the unpredictability taught in the art with regard to titin mutations and heart disease. Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the unpredictability in the art.

The response asserts that the teachings of Itoh Satoh confirm that the experimentation required is not undue, and that the experiments of Itoh-Satoh do not negate the fact that detection of mutations in the titin gene can be correlated with diseases or conditions of the heart without undue experimentation. With regard to Garvey et al, the response asserts that it is understood that not every mutation in titin will lead to a disease or condition of the heart, but that Applicants have shown that this protein is importation for proper function and development of the heart and that the present discovery forms basis for diagnosis of diseases or conditions of the heat based on mutations of this gene. These argument has been thoroughly reviewed but were not found persuasive. The teachings of Itoh-Satoh exemplify that associating any mutation in the titin gene with any disease or condition of the heart, risk of disease or condition, as well as facilitating the etiology of any disease or condition of the heart, is unpredictable (Itoh-Satoh teaches that a mutation exists in the titin gene which results in an altered titin protein sequence and that such is not associated with dilated cardiomyopathy, a disease or condition of the heart). Therefore,

given that the specification has only taught a single mutation in a zebrafish titin gene and has not correlated how this mutation would be associated with any disease or condition of the heart, such as hypertension or coronary artery disease, in any titin gene, variant or homolog, the specification does not enable the full scope of the claimed invention. The response asserts that Siu et al supports the enablement of the claims because Siu et al shows that undue experimentation is not required to determine whether any particular mutation is associated with disease. This argument has been thoroughly reviewed but was not found persuasive because the teachings of Siu do in fact show that one of skill in the art, based on the specification's extremely limited disclosure and guidance, would not be able to predict which mutations were associated with, or indicative of risk or likelihood of a heart disease or condition or would facilitate in determining the etiology of an existing heart condition. However, such knowledge would be required of the skilled artisan to practice the invention as broadly as it is claimed. To practice the invention as broadly as it is claimed, the skilled artisan would have to perform trial and error analysis to determine which of the large number of possible mutations in any titin gene is associated with any specific disease or condition of the heart, including heart failure. As Itoh-Satoh and Siu exemplifies that such analysis is unpredictable as to which mutations have a significant effect versus not, such analysis is considered undue.

In response to the previous office action's comments regarding conservation among species, the response asserts that it is not unusual for there to be differences between sequences of a different species for any given gene and that determination of whether a mutation exists is done by comparison with a naturally occurring sequence of the gene and that claims 5 and 29 specify that the test subject is human. This argument has been thoroughly reviewed but was not

found persuasive as the specification provides no teaching or guidance as to which mutations in humans would be diagnostic for, predictive of, or provide information regarding etiology of a disease or condition of the heart. The basis for these factors in the rejection set forth above, was to highlight the fact that the specifications teachings were deficient in providing the skilled artisan with guidance to correlate the single phenotype observed in zebrafish to the enormous number of mutations encompassed by the scope of the claims. With regard to the response's comments regarding a universal correlation, it is noted that the office action has not required that a universal correlation must exist, but that the specification has not established that one exists so that the skilled artisan would be able to predictably determine that the mere presence of a mutation in titin would indicate that a subject had, was at risk, may have, may be at risk, had an increased likelihood of developing any titin related disease or condition of the heart, or that the mere presence of a mutation in titin would facilitate in determining the etiology of an existing heart condition. Given the lack of guidance from the specification and the art, the skilled artisan would be required to test subjects as well as mutations using trial by error experimentation to determine mutations which are associated with disease, or predictive of disease risk, or provide information regarding disease etiology. The claims, in addition to the newly added claims are not drawn to screening for mutations which may be associated with disease, but are drawn to determining whether a subject, from any species, has a disease, or is at risk for disease, or may have a disease or may have an increased likelihood of developing a titin related disease or condition of the heart, as well as to methods of facilitating determination of the etiology of an existing heart condition, simply by detecting any mutation in titin. However, the specification provides no guidance as to which mutations will achieve such results, which knowledge is

required for the skilled artisan to practice the invention commensurate in scope with the claims. While, the specification has taught a single mutation that appears to be associated with a weak heart beat in zebrafish embryos, such a teaching is insufficient to provide one of skill in the art with a predictable correlation that any substitution, deletion or insertion in the titin gene, or more specifically the IS3 fragment of N2B would result in or provide an indication of risk of a weak heartbeat in zebrafish embryos or any other subject, let alone any disease or condition of the heart, including heart failure. The claims encompass any mutation in any titin gene, which are not necessarily predictably correlated to any disease or condition of the heart as exemplified by the teachings of Itoh-Satoh and Siu. The recitation of "disease or condition of the heart" encompasses a large number of diseases or conditions which are not necessarily a result of a weak heartbeat. For example, although the phenotype of the zebrafish, that is a weak heartbeat, may be similar to mammalian heart failure, such is not necessarily diagnostic of mammalian heart failure, let alone any disease or condition of the heart. In other words, while a weak heart beat may lead to heart failure, there are other causes for heart failure including coronary artery disease, hypertension and diabetes (as taught by the specification at page 1). Therefore, while coronary artery disease, hypertension, or diabetes may all lead to heart failure, a mutation which is associated with any one of such risk factors is not necessarily *diagnostic* of another. Each risk factor represents specific diseases which have different causes in and of themselves. As noted in the previous office action, it is known for nucleic acids as well as proteins that a single nucleotide or amino acid change or mutation can alter the function of the biomolecule in some instances. The effects of these changes, however, are unpredictable as to which ones have a significant effect versus not, as exemplified by the teachings of Itoh-Satoh and Siu. The

specification has not provided the skilled artisan with any teaching or guidance as to which nucleotide or amino acid positions in the titin gene would be responsible for normal or aberrant activity of the titin protein, such that the skilled artisan would be able to predictably correlate which mutations would have an effect on the function or activity of any titin protein and therefore be able to determine which mutations would be predictably diagnostic of, or provide information regarding disease risk or etiology, for any specific disease or condition of the heart, including heart failure.

Written Description

5. Claims 1-6, 20 and newly added claims 21-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to a method for determining whether a test subject from any source, including mammals and humans, has, is at risk of developing, may have or may be at risk of developing, or has an increased likelihood of *any* titin related disease or condition of the heart by detecting *any* mutation from a titin gene, including a naturally occurring gene. The claims are further drawn to a method of facilitating the etiology of an existing heart disease or condition by detecting *any* mutation from a titin gene , from any source. The claims are further limited to heart failure as well as any mutation in a cardiac specific exon as well as the N2B exon of titin.

The specification teaches that a during a mutation screening of zebra fish, a phenotype resulting from mutation of the titin gene was observed which was similar to mammalian heart failure (page 1). The specification teaches that the claimed recitation of a "titin gene" is drawn to a nucleic acid that encodes a titin protein or polypeptide that has 45%, 60%, 75% and 90% identity to the sequence of human or zebra fish titin molecules (see p. 3). Such a recitation encompasses mutants, allelic variants, and homologs of titin from any source, which have not been taught or described in the specification. The specification further defines "titin related disease or condition" to mean a disease or condition that results from an inappropriately high or low expression of a titin gene or a mutation in a titin gene that alters the biological activity of a titin nucleic acid or polypeptide. Therefore, the recitation encompasses any substitution, deletion or insertion in any titin gene. The specification asserts that the methods include diagnostic assessment of heart disease, heart failure (page 8, first full para), congestive heart failure, and coronary artery diseases or conditions associated with valve formation defects (page 9). The specification, however, has only taught a single mutation in the N2B exon of titin that was found in zebra fish embryos characterized with a weak heartbeat (see p. 20). Further, the whereabouts of this mutation in the N2B exon are unclear as the specification only teaches that identification of a T-G transition in the *pikm171* allele was found which resulted in a change of leucine in the IS3 fragment of N2B domain into a stop codon. The specification, however, does not teach at which leucine residue this mutation occurs. In addition, the specification does not define the specific genotype of the *pickwick* mutation. The specification recites "a mutation in a cardiac specific exon, such as the N2B exon, e.g. the *pickwick* mutation" (see p. 2, lines 9-10), thus it is unclear from this recitation or the teachings in the specification as to what is

encompassed by the *pickwick* mutation. Xu (Xu et al; Nature Genetics, vol. 30, pages 205-209; 2002) teaches that there are multiple alleles in the *pik* complementation group (see abstract), however the specification provides no description of the other alleles. This recitation, therefore, appears to encompass any mutation with the *pickwick* phenotype (p. 19, lines 4-5). The specification, however, has only taught a single mutation that appears to be associated with a weak heart beat in zebra fish embryos, but the specific genotype of this mutation is not taught.

The specification provides insufficient written description to support the genus of titin genes or mutations encompassed by the claims. The claims encompass a large genus of nucleic acids which comprise mutations in any region of a titin gene from any species. The genus includes an enormous number of polymorphisms and mutations for which no written description is provided in the specification. For example, the art of Itoh-Satoh provides for mutation which have not been taught or described in the specification in any way. The large genus encompassed by the claimed is represented in the specification by only the generally described single mutation which is associated with the "pickwick" phenotype. The specification does not teach the specific location of this mutation in the titin gene from zebra fish nor does it teach what a corresponding position would be in any other species. Thus, applicant has express possession of only a single undefined mutation in a genus which comprises hundreds of millions of different possibilities. Here, no common element or attributes of the sequences are disclosed which would permit selection of sequences as polymorphisms or mutations. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations of associating a polymorphism with diagnosis of or indicative of increased risk of developing any disease or condition of the heart.

Further, these claims expressly encompass allelic variants including insertions, deletion, substitutions and transversions at thousands of different sites. However, no predictable correlation between the structural alterations of the single polymorphism and heart disease is provided by the specification. Therefore, the skilled artisan would be unable to predictably correlate any other structural change in any other region of titin from "any" species and an association with any disease or condition of the heart as is broadly claimed. Additionally, claim 7 is drawn to "the pickwick" mutation, but the specification provides no clear definition of what mutations are encompassed by the term "pickwick" or the specific location of the single polymorphism taught in the specification.

The specification provides no correlation between the structure of mutations in titin and the function of such mutations with diseases or conditions of the heart. The mutation shown is not representative of the enormous genus of structurally and functionally distinct mutations which would be associated with the large number of different diseases and conditions of the heart because it is not known which mutations would have the same affect.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number'' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.) In the instant case, the specification fails to teach the necessary common attributes or features of the genus of encompassed nucleic acids and

mutations in view of the single species disclosed. As such, one of skill in the art would not recognize that applicant was in possession of the genus of nucleic acids and polymorphisms encompassed by the broadly claimed invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed nucleic acids and mutations, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. The current situation is a definition of the compound solely based on its functional utility, as a polymorphism, without any definition of the particular polymorphisms claimed.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it

obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

Response to Arguments

6. The response traverses the rejection. The response asserts that the amendment to claim 1 to specify a "naturally occurring titin gene" overcomes the examiner's basis for rejection regarding the definition of "titin gene" given in the specification. This amendment and argument have been thoroughly reviewed but was not found persuasive. The term "naturally occurring titin gene" encompasses titin genes from any species. In the previous office action, the examiner stated that the term "titin gene" as defined by the specification, encompasses mutants, allelic variants, and homologs of titin from any source. "Any source" includes any species, which is still an extremely large number of possible allelic variants, mutants, and homologs of any titin gene, which is encompassed by the amended claims and does not narrow the scope of the claims sufficiently to overcome the rejection.

The response also asserts that the present claims are drawn to methods of diagnosing diseases or conditions of the heart by detection of mutations in titin genes and not to mutant titin genes themselves. The response further asserts that the statements regarding that the nucleic acid is required is more appropriate in a rejection of claims to nucleic acids or proteins and not to methods that involve the detection of mutations. These arguments have been thoroughly reviewed but were found unpersuasive. The basis for the rejection made in the previous office action is with regard to the large genus of undisclosed diagnostic mutations (diagnostic for

disease, risk of disease, or information regarding etiology of an existing heart condition) in the large number of undisclosed titin genes, variants, and homologs from any species encompassed by the claims. In this case, although the methods involve assessement, the claims are not simply drawn to methods for detecting a mutation in a gene, but are specifically drawn to and encompass *determining whether any subject has or is at risk of developing, or may have or be at risk of developing, or is at increased risk of developing,* as well as to methods of *facilitating the etiology of an existing* titin related disease or condition of the heart by detecting mutations in *any* titin gene, variant, or homolog. The specification has only taught a single titin nucleic acid (human) and the mutation characteristic of a weak heartbeat in zebrafish taught in the specification is not in the human sequence provided, but the titin gene of a zebrafish. This single mutation is not representative of the large genus of possible diagnostic or risk associated mutations of any titin related disease or condition of the heart, in the large number of undisclosed titin genes, variants, and homologs in any species which are encompassed by the claimed methods, nor does this single phenotype provide any guidance regarding information as to disease etiology of the extremely broad genus of mutations encompassed by the claims.

The response further asserts that methods of diagnosing diseases or conditions of the heart by detection of mutations in titin gene are adequately described in the specification, which describes obtaining samples from patients and analysis of titin sequences, and that it is not necessary for the specification to list every possible mutation that could be associated with these diseases or conditions as they can be easily identified by comparison with sequences from healthy controls. These arguments have been thoroughly reviewed but were not found persuasive. While the specification provides general description of how to detect mutations in

known sequences, the *claims* are drawn to detecting a large number of possible undescribed diagnostic mutations (for any disease or condition of the heart) in a large number of undisclosed and undescribed titin genes, variants, and homologs, in any species. The rejection in the previous office action did not require that every possible mutation that could be associated with these diseases, or that every possible titin sequence, be identified or disclosed. Rather, the rejection stated that "[the mutation taught in the specification] is not representative of the large number of substitutions, deletions, and insertions in any [naturally occurring] titin gene from any source that are encompassed by the claimed invention." With regard to specific mutations, the specification, however, has only taught a single mutation in the N2B exon of titin that was found in zebrafish embryos characterized with a weak heartbeat (see p. 20). The whereabouts of this mutation in the N2B exon are unclear as the specification only teaches that identification of a T-G transition in the *pikm171* allele was found which resulted in a change of leucine in the IS3 fragment of N2B domain into a stop codon, however the specific leucine residue where this mutation occurs, is not taught. This single mutation is not representative of the extremely large genus of possible undisclosed diagnostic mutations (of any disease or condition of the heart), in the large number of undisclosed titin genes, variants, and homologs from any species, including humans, which are encompassed by the claimed methods.

7. Claims 1-6, and 20-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

The claims have been amended to recite, "may have or be at risk of developing", however the specification does not appear to provide support for this amendment. It appears the amendment has been made to alter the scope encompassed by the claims, however it is unclear how "may have or be at risk of developing" is different in scope than "risk of developing". In other words, what is the change in scope encompassed by determining that someone or some subject is "at risk of developing" vs determining that they "may have" or "may be at risk of developing" a disease or condition. The specification asserts, at page 7, that the diagnostic methods make it possible to detect "an increased likelihood of heart disease". At page 8, the specification recites "diagnostic methods can be used with patients that have not yet developed heart failure but who are at risk of developing such a disease, or with patients that are at an early stage of developing such a disease". At page 9, the specification asserts that the methods can be used to identify parents who may be carriers of a recessive titin mutation. However, none of these recitations provide for diagnostic methods of subjects who "may have or [may] be at risk of developing a titin related disease or condition...". The specification provides no support for this new recitation nor does it provide any guidance as to how to assess this apparent attempt at alteration in claimed scope. Accordingly, the amendment appears to have introduced new matter into the claimed invention.

Response to Arguments

8. The response traverses the rejection and points to the specification at page 7, lines 1-3, "it is possible to detect an increased likelihood of heart disease" as support for the use of the term

"may" and further asserts that "increased likelihood" indicates an increased chance of disease which is consistent with the use of the term "may". These arguments have been thoroughly reviewed but were not found persuasive. While there is no requirement that a term literally be supported by a specification, in this instance, the change in scope is not clearly defined by the specification, such that there is no guidance in the specification as to how "risk of developing", "may have or may be at risk of developing", or "increased likelihood" are differentiated from each other. In other words, the specification provides no guidance as to how the skilled artisan would determine that a subject "may be at risk of developing" a disease rather than would be "at risk of developing a disease". Although newly added claims 23 is supported by the disclosure, the specification provides no guidance that "increased likelihood of developing disease" is the same scope as a subject who "may" be at risk of developing disease. The rejection is therefore maintained.

Claim Rejections - 35 USC § 102

9. Claims 1-6, 20, 21, and 23-31 are rejected under 35 U.S.C. 102(a) as being anticipated by Satoh et al (Biochemical and Biophysical Research Communications, vol. 262, pp 411-417, 1999).

With regard to claims 1, 4-6, 20, 21, 23-25, and 28-31, Satoh teaches of an A to T transversion in codon 740 of the titin gene of a human patient with hypertrophic cardiomyopathy, which replaces an Arginine with Leucine (see abstract). Satoh teaches that this mutation was not found in more than 500 normal chromosomes (see abstract). With regard to claims 2, 3, 26 and 27, Satoh teaches that genomic DNA was extracted from each subject and

that PCR primers flanking each exon of the titin gene were designed to amplify each exon (p. 412-col. 1, "PCR-DCP analysis") and that to identify the mutation in exon 14, the PCR product was cloned into a vector and sequenced (para. bridging cols 1 and 2, p. 412).

Response to Arguments

10. The response requests that the rejection be withdrawn in view of an accompanying Declaration by inventor Xialei Xu, which was submitted in the parent application. The response asserts that applicants established a connection between a mutation causing a weak heartbeat in the titin gene and thus reduced the invention to practice, prior to the publication date of the Satoh reference. It is noted that no declaration was submitted with the instant response and that Affidavits or declarations, such as those submitted under 37 CFR 1.130, 1.131, and 1.132, filed during the prosecution of the prior application do not automatically become a part of this application. Where it is desired to rely on an earlier filed affidavit or declaration, the applicant should make the remarks of record in this application and include a copy of the original affidavit or declaration filed in the prior application. The rejection is therefore maintained.

Conclusion

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. No claims are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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1/5/07